Effect of *Helicobacter pylori* Treatment on Long-term Mortality in Patients with Hypertension

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Background/Aims: A meta-analysis of randomized trials performed in healthy asymptomatic individuals suggested that overall mortality may increase after *Helicobacter pylori* eradication despite a significant decrease in the gastric cancer incidence and mortality rates. This retrospective population-based cohort study investigated if *H. pylori* treatment is associated with an increase in overall mortality in patients with hypertension. **Methods:** From the database of the Korean National Health Insurance Sample Cohort, we selected 198,487 patients treated for hypertension between 2002 and 2010. Those who received *H. pylori* treatment (*H. pylori* treatment cohort, 5,541 patients) were matched to those who did not (nontreatment cohort, 11,082 patients) at the ratio of 1 to 2. The primary outcome was the risk of overall mortality. The secondary outcomes were the risks of mortality due to cardiovascular disease, cerebrovascular disease, and cancer. The outcomes were evaluated from 6 months after *H. pylori* treatment to December 2013. A Cox proportional hazard model was used to estimate the hazard ratios (HRs). **Results:** During a median follow-up period of 4.8 years, death from any cause was reported in 4.1% of the patients in the *H. pylori* treatment cohort and 5.5% of the patients in the nontreatment cohort. The adjusted HR (aHR) for overall mortality in the *H. pylori* treatment cohort was 0.70 (95% confidence interval [CI], 0.60 to 0.82; p<0.001). With regard to cause-specific mortality, compared with the nontreatment cohort, the *H. pylori* treatment cohort had a lower risk of mortality due to cerebrovascular disease (aHR, 0.46; 95% CI, 0.26 to 0.81; p=0.007). The risks of mortality due to cancer and cardiovascular disease were not different between the cohorts. **Conclusions:** *H. pylori* treatment is not associated with an increase in overall mortality in patients treated for hypertension. **(Gut Liver 2020;14:47-56)**

INTRODUCTION

Helicobacter pylori infection is an important risk factor for gastric cancer and is categorized as a group I carcinogen.[1] A meta-analysis of six randomized trials performed in asymptomatic individuals reported that *H. pylori* eradication reduced gastric cancer incidence (relative risk, 0.66) and mortality (relative risk, 0.67).[2] This meta-analysis, however, showed an approximately 9% nonsignificant increase in overall mortality after *H. pylori* treatment.[2] Although the detailed causes of death were not available from these studies, cardiovascular, cerebrovascular, or other cancer mortalities could be the major causes of death according to worldwide statistics.[3-5]

H. pylori treatment regimens consist of a combination of broad-spectrum antibiotics, including amoxicillin, clarithromycin, tetracycline, or metronidazole.[6] Among those antibiotics, concerns about a link between clarithromycin use and cardiovascular mortality have been reported. A randomized trial performed in patients with stable coronary heart disease showed that short-term clarithromycin treatment (2 weeks) significantly increased cardiovascular mortality during a 3-year follow-up and overall mortality during a 6-year follow-up.[7,8] In a meta-analysis including 33 studies investigating the associations

between macrolide antibiotics and cardiovascular risk, clarithromycin was significantly associated with increased cardiovascular disease mortality and overall mortality.[9] Antibiotic treatment also causes disruption of gut microbiota (dysbiosis), which could affect various steps in the process of carcinogenesis (cancer initiation, progression, and dissemination) or disrupt the efficacy of anti-cancer treatments.[10,11] A recent nested case-control study using a UK medical records database reported a possible association between repeated macrolide antibiotics use and increased risk of various types of cancers.[12]

Hypertension is an important risk factor for death from cardiovascular and cerebrovascular diseases.[13] Thus, we selected patients with hypertension from the database of the Korean National Health Insurance population-based sample cohort. In the present study, we investigated if *H. pylori* treatment in patients with hypertension is associated with overall mortality or with mortality from major causes.

MATERIALS AND METHODS

1. Study design and data source

This study is a retrospective population-based cohort study using the Korean National Health Insurance Service-National Sample Cohort database. This study was approved by the Institutional Review Board of the National Cancer Center, Korea (IRB number: NCC2016-0043) and informed consent requirements for the individuals in the database were waived.

We selected a study population from the database,[14] which is a population-based sample cohort established to provide representative and useful health insurance and health examination data to public health researchers and policymakers. To summarize this cohort, approximately one million subjects (2.2% of the total eligible population) were randomly sampled from the 2002 Korean National Health Insurance database and followed up until 2013. This database has been well-validated and increasingly used for epidemiological and health policy studies for general Korean populations.[15,16]

The database includes participants' insurance eligibility, medical treatments, medical care institutions, and general health examinations data. In the insurance eligibility database, variables include the participant's identity and socioeconomic information (gender, residential area, type of health insurance, level of income, birth, and death). The medical treatment database contains the participant's medical treatment bills, bill details, details of disease, and prescriptions. The general health examination database includes major health exam results and information about lifestyles and behaviors from questionnaires.[14] To identify subjects' diagnosis and cause of mortality, disease codes from the International Classification of Diseases (ICD) 10th revision were used.[17]

2. Study population

We selected patients with hypertension from the database. Patients who were aged ≥20 years, diagnosed with hypertension (ICD-10 code, I10) between 2002 and 2010, and had been prescribed at least a one anti-hypertensive drug were included in our study as patients with hypertension.

The prescription of *H. pylori* treatment regimens–proton-pump inhibitor (PPI)-clarithromycin-containing triple therapy (PPIs, clarithromycin, and amoxicillin) or bismuth-containing quadruple therapy (bismuth, PPIs, metronidazole, and tetracycline)–was examined using drug codes. In Korea, those treatment regimens were approved as the first-line and the second-line treatment, respectively, by the guidelines and National Health Insurance.[18] The *H. pylori* treatment cohort included patients who were prescribed *H. pylori* treatment regimens after a hypertension diagnosis up to June 2013.

Patients in the *H. pylori* treatment cohort were matched with those in the nontreatment cohort at a ratio of 1:2 using the simple random sampling without replacement method. Variables of age group, sex, hypertension diagnosis date (month and year) and Charlson comorbidity index (CCI) score[19] at the time of hypertension diagnosis were included for matching.

Of the patients in the *H. pylori* treatment cohort, patients who died from any cause or those who were diagnosed with any cancers, cardiovascular diseases, or cerebrovascular diseases before or within the 6 months after *H. pylori* treatments were excluded. In the nontreatment cohort, we also excluded patients who died due to any causes or those who were diagnosed with any cancers, cardiovascular diseases, or cerebrovascular diseases before or within 6 months after the corresponding date for *H. pylori* treatment prescription of the matched case.

3. Observation periods

To define the starting time of observation periods for study outcomes in the nontreatment cohort, the corresponding date of *H. pylori* treatment prescription in the treatment cohort was assigned to each patient in the nontreatment cohort after matching. Thus, the observation period was started from the date of *H. pylori* treatment prescription in the treatment cohort and the corresponding date in the nontreatment cohort. These observation periods were continued until December 2013 (Supplementary Fig. 1).

4. Study outcomes

The primary outcome was overall mortality, defined as a death from any cause occurring from 6 months after the starting time of the observation period. Secondary outcomes included cancer-specific mortality, cardiovascular disease-specific mortality, and cerebrovascular-specific mortality occurring from 6 months after the starting time of the observation period. The disease codes describing the cause of death in the database

were identified to define disease-specific mortalities, and disease codes were ICD-10 code C00-97 for cancers, I20-I25 for cardiovascular diseases, and I60-I66 for cerebrovascular diseases (Supplementary Table 1).

5. Statistical analysis

Descriptive analyses were performed to compare patients' baseline characteristics between the *H. pylori* treatment cohort and nontreatment cohort. The Student t-test and chi-square test were used to compare differences between cohorts.

Kaplan-Meier curves with log-rank test were performed for the comparisons of overall mortality and cause-specific mortalities between *H. pylori* treatment and nontreatment cohorts. Univariate and multivariate Cox proportional hazard models were used to estimate hazard ratios (HR) with 95% confidential interval (CI) for mortalities and incidences of cancers, cardiovascular, and cerebrovascular diseases according to the *H. pylori* treatment. Covariates included for the multivariate analysis were age group, sex, economic status, residential area, CCI scores, and the use of aspirin and statin. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). p-values of <0.05 were considered statistically significant.

RESULTS

1. Baseline characteristics of the study population

The study flow is presented in Fig. 1. A total of 198,487 patients were diagnosed with hypertension and prescribed hypertension medication at least once. Of these, 9,552 patients were prescribed *H. pylori* treatment regimens between the hypertension diagnosis and June 2013. After excluding 3,661 patients who died or were diagnosed with cancer, cardiovascular, or cerebrovascular diseases before or within 6 months of *H. pylori* treatment to exclude preexisting conditions, 5,891 patients were included for case-control matching. A total of 5,541 patients in the *H. pylori* treatment cohort and 11,082 matched patients in the nontreatment cohort were included for the final analyses.

In the *H. pylori* treatment cohort, 96.4% of patients were prescribed with PPI-clarithromycin-containing triple therapy (Table 1). Baseline characteristics were similar between the two co-
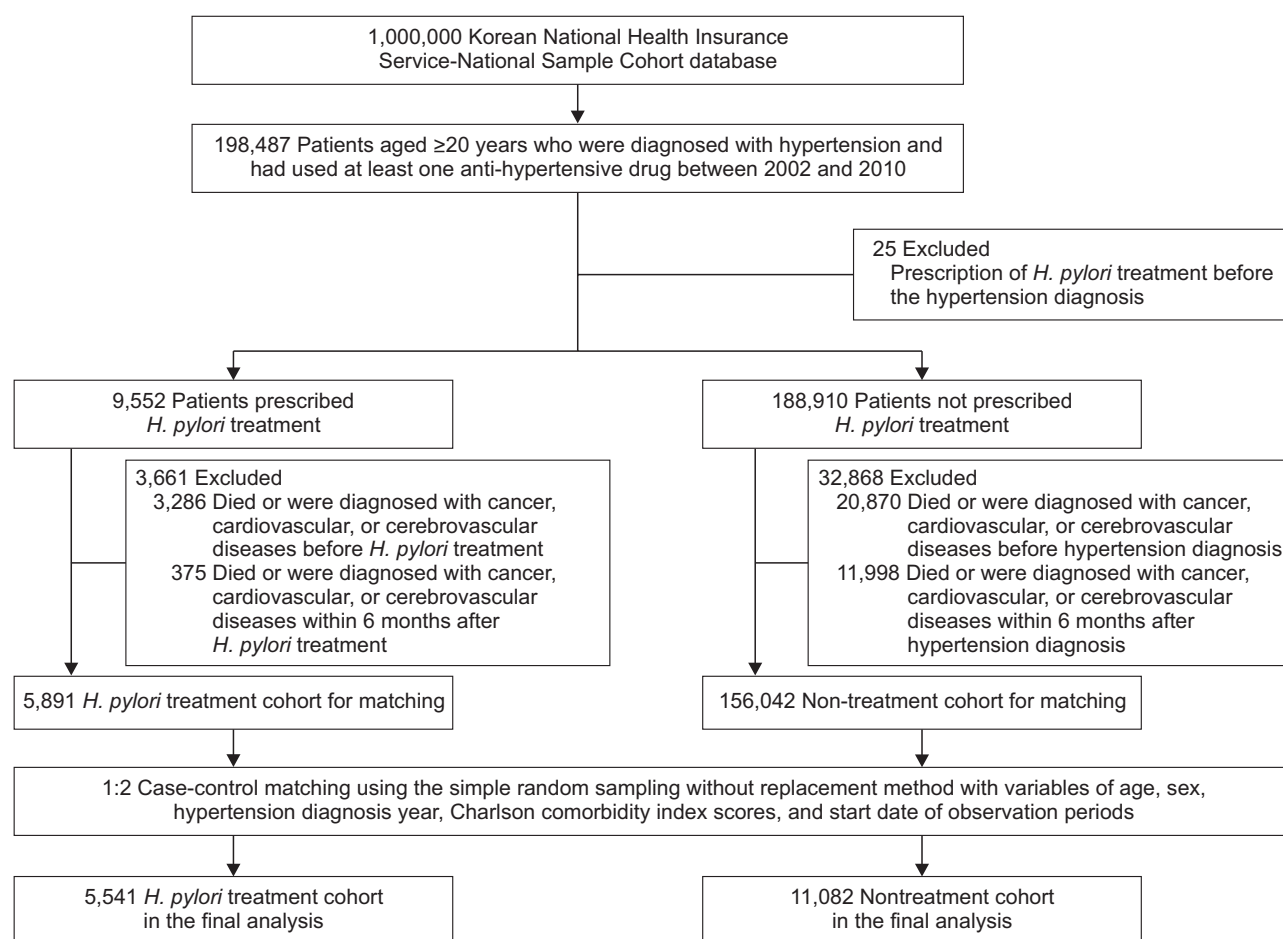
Fig. 1. Study flowchart. Patients with hypertension who had used at least one anti-hypertensive drug were sorted into the *Helicobacter pylori* treatment cohort or nontreatment cohort. Patients in the *H. pylori* treatment cohort were matched with those in the nontreatment cohort at the ratio of 1 to 2 by using simple random sampling without replacement.

Table 1. Baseline Characteristics of the Study Population

Characteristic	*H. pylori* treatment cohort (n=5,541)	Nontreatment cohort (n=11,082)	p-value
Age, yr			1.00
20–29	41 (0.7)	82 (0.7)	
30–39	424 (7.7)	848 (7.7)	
40–49	1,526 (27.5)	3,052 (27.5)	
50–59	1,968 (35.5)	3,936 (35.5)	
60–69	1,297 (23.4)	2,594 (23.4)	
70–79	268 (4.8)	536 (4.8)	
≥80	17 (0.3)	34 (0.3)	
Sex			1.00
Male	3,059 (55.2)	6,118 (55.2)	
Female	2,482 (44.8)	4,964 (44.8)	
Residential area			<0.001
Metropolitan	2,745 (49.5)	5,180 (46.7)	
Small city or rural	2,796 (50.5)	5,902 (53.3)	
Economic status level, %			<0.001
0–50	2,060 (37.2)	4,452 (40.2)	
51–100	3,481 (62.8)	6,630 (59.8)	
Smoking			<0.001
Never smoker	2,574 (46.5)	4,652 (42.0)	
Ex-smoker	520 (9.4)	844 (7.6)	
Current smoker	1,045 (18.9)	1,520 (13.7)	
Missing	1,402 (25.3)	4,066 (36.7)	
Alcohol drinking			0.863
Never drinking	2,383 (43.0)	4,002 (36.1)	
1–2 times/wk	1,245 (22.5)	2,127 (19.2)	
3–4 times/wk	414 (7.5)	733 (6.6)	
5–7 times/wk	245 (4.4)	425 (3.8)	
Missing	1,254 (22.6)	3,795 (34.2)	
Body mass index, kg/m^2			0.204
≤18.5	46 (0.8)	95 (0.9)	
18.6–22.9	1,065 (19.2)	1,845 (16.6)	
23.0–24.9	1,208 (21.8)	1,934 (17.5)	
≥25.0	2,051 (37.0)	3,556 (32.1)	
Missing	1,171 (21.1)	3,652 (33.0)	
CCI score at the time of hypertension diagnosis			1.00
0	2,955 (53.3)	5,910 (53.3)	
1	866 (15.6)	1,732 (15.6)	
≥2	1,720 (31.0)	3,440 (31.0)	
Aspirin use*			0.21
No	4,386 (79.2)	8,864 (80.0)	
Yes	1,155 (20,8)	2,218 (20.0)	
Statin use*			<0.001
No	4,513 (81.4)	9,434 (85.1)	
Yes	1,028 (18.6)	1,648 (14.9)	
H. pylori treatment regimen			
PPI-clarithromycin containing triple therapy	5,342 (96.4)	-	
Bismuth-containing quadruple therapy	72 (1.3)	-	
Both	127 (2.3)	-	
Follow-up period, yr	4.8 (2.6-7.4)	4.8 (2.6-7.3)	0.216

Data are presented number (%) or median (interquartile range).
H. pylori, *Helicobacter pylori*; CCI, Charlson comorbidity index; PPI, proton-pump inhibitor.
*Patients who used aspirin and statin were defined as those who were prescribed the drugs for at least 30 days.

horts, except that patients in the *H. pylori* treatment cohort had a higher proportion of residency in metropolitan areas (49.5% vs 46.7%, p<0.001) and statin use (18.6% vs 14.9%, p<0.001) than those in the nontreatment cohort.

2. Risk of overall mortality after *H. pylori* treatment

During the observation periods until December 2013 (median, 4.8 years; interquartile range, 2.6 to 7.3 years; 85,078 person-years), death occurred in 837 patients (5.0%); 229 patients (4.1%) in the *H. pylori* treatment cohort and 608 (5.5%) in the nontreatment cohort. Overall survival in the *H. pylori* treatment cohort was significantly higher when compared with that in the nontreatment cohort (p<0.001 by the log-rank test) (Fig. 2). The 5-year overall survival rates were 96.7% in the *H. pylori* treatment cohort and 95.3% in the nontreatment cohort. A multivariate analysis also showed a significantly reduced risk for overall mortality in the *H. pylori* treatment cohort with an adjusted HR of 0.70 (95% CI, 0.60 to 0.82; p<0.001) (Table 2). Other significant risk factors associated with increased overall mortality were age ≥60 years, male sex, economic status level lower than 50%, and CCI scores of 1 and ≥2 (vs CCI score 0).

3. Risk of cardiovascular disease, cerebrovascular disease, and overall cancer incidence considering *H. pylori* treatment

Table 3 shows the incidence risks of diseases related to common cause of deaths, including cancer, cardiovascular, and cerebrovascular diseases, according to *H. pylori* treatment. In the *H. pylori* treatment cohort, risk for cardiovascular disease incidence (adjusted HR [aHR], 1.13; 95% CI, 1.03 to 1.24; p=0.01) and overall cancer incidence (aHR, 1.14; 95% CI, 1.01 to 1.28; p=0.035) were significantly higher when compared with

the nontreatment cohort. No significant difference in the risk for cerebrovascular disease incidence was found. According to cancer type, the *H. pylori* treatment cohort had significantly increased risks of colorectal cancer (aHR, 1.39; 95% CI, 1.01 to 1.90; p=0.043) and thyroid cancer (aHR, 1.54; 95% CI, 1.03 to 2.32; p=0.037).

4. Risk of mortalities due to cardiovascular disease, cerebrovascular disease, and overall cancer according to *H. pylori* treatment

The mortality risk due to cerebrovascular disease was significantly lower in the *H. pylori* treatment cohort (aHR, 0.46; 95% CI, 0.26 to 0.81; p=0.007) compared with the nontreatment cohort. However, mortality risk due to cardiovascular disease (aHR, 0.96; 95% CI, 0.54 to 1.71; p=0.896) and cancer (aHR, 0.76; 95% CI, 0.57 to 1.01; p=0.058) were not significantly different between the *H. pylori* treatment and control cohorts. No significant association between *H. pylori* treatment and mortality risk of gastric cancer was found (aHR, 1.21; 95% CI, 0.44 to 3.38; p=0.71). However, as compared with the control group, mortality risk due to non-gastric cancers were significantly decreased (aHR, 0.73; 95% CI, 0.55 to 0.99; p=0.04), especially liver cancer-specific mortality (aHR, 0.48; 95% CI, 0.25 to 0.91; p=0.024) (Table 4).

DISCUSSION

In this retrospective population-based cohort study, we investigated the effects of *H. pylori* treatment on overall mortality as well as major causes of death. We found that *H. pylori* treatment in hypertension patients was associated with a significant decrease in the risk of overall mortality and cerebrovascular disease mortality. There was no association between *H. pylori* treatment and mortality risk due to cardiovascular diseases and overall cancers.

The recent European guideline stated that *H. pylori* eradication reduces the risk of gastric cancer development.[6] A meta-analysis showed that the overall mortality rate after *H. pylori* treatment was increased by 9%, despite reduced gastric cancer incidence and gastric cancer mortality.[2] The finding suggests that non-gastric cancer-related mortalities might be increased after *H. pylori* treatment. We also recently reported that metachronous gastric cancer risk (HR, 0.50; p=0.03) was significantly reduced in early gastric cancer patients who underwent endoscopic resection, but overall mortality risk after *H. pylori* treatment was increased (HR, 1.95; p=0.19).[20] However, these studies evaluated overall mortality as a secondary outcome and found no significant differences.[2,20] In our study, overall mortality was evaluated as the primary outcome, and we found that *H. pylori* treatment was not associated with increased overall mortality in patients with hypertension.

Clarithromycin is often included in several *H. pylori* treatment
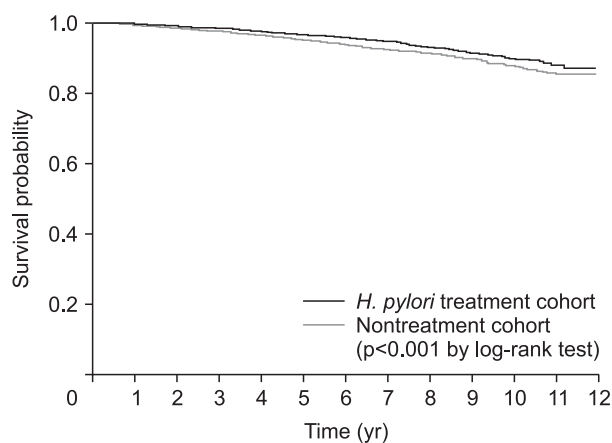

Fig. 2. Overall survival curves according to *Helicobacter pylori* treatment. During the follow-up period, death was reported in 229 patients (4.1%) in the *H. pylori* treatment cohort and 608 (5.5%) in the nontreatment cohort. The overall survival rate of the *H. pylori* treatment cohort was significantly higher than that of the nontreatment cohort.

Table 2. Risk Factors Associated with Overall Mortality

Risk factor	No.	Univariate analysis*		Multivariate analysis*,[†]	
		Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Age, yr			<0.001		<0.001
<60	11,877	1.00		1.00	
≥60	4,746	3.99 (3.46–4.59)		4.02 (3.05–4.64)	
Sex			<0.001		<0.001
Female	9,177	1.00		1.00	
Male	7,446	1.60 (1.39–1.84)		1.75 (1.52–2.02)	
Economic status level, %			<0.001		<0.001
0–50	6,512	1.00		1.00	
51–100	10,111	0.75 (0.66–0.86)		0.76 (0.66–0.87)	
Residential area			0.003		0.064
Metropolitan	7,925	1.00		1.00	
Small city or rural	8,698	1.23 (1.07–1.41)		1.14 (0.99–1.31)	
CCI score					
0	8,658	1.00		1.00	
1	2,952	1.37 (1.13–1.66)	0.001	1.27 (1.04–1.54)	0.018
≥2	5,040	1.82 (1.56–2.11)	<0.001	1.80 (1.55–2.10)	<0.001
H. pylori treatment			<0.001		<0.001
No	11,082	1.00		1.00	
Yes	5,541	0.74 (0.64–0.86)		0.70 (0.60–0.82)	
Aspirin use			0.922		0.16
No	13,250	1.00		1.00	
Yes	3,373	1.01 (0.85–1.19)		0.88 (0.75–1.05)	
Statin use			0.094		0.097
No	13,947	1.00		1.00	
Yes	2,676	0.83 (0.67–1.03)		0.83 (0.66–1.03)	

HR, hazard ratio; CI, confidence interval; CCI, Charlson comorbidity index; *H. pylori*, *Helicobacter pylori*.
*Analyses were performed using the Cox proportional hazard model; [†]Covariates for multivariate analysis were age, sex, economic status, residential area, CCI score, *H. pylori* treatment, and aspirin and statin use.

regimens, such as PPI-clarithromycin-containing triple therapy, concomitant therapy, and sequential therapy, which are recommended as the first-line treatment regimens.[6,18,21] Clarithromycin has been reported to be associated with increased cardiovascular mortality risk, especially in the short-term periods after the start of the drugs, because of arrhythmia-related cardiovascular events.[22,23] In addition, a prospective randomized trial reported that 2 weeks' clarithromycin treatment significantly increased long-term overall mortality until 10-year follow-up.[7,8,24] However, the mechanisms of the increased long-term mortality risk after clarithromycin use are not clearly elucidated. In our study, however, overall mortality and cardiovascular disease mortality were not increased, even though most patients (96.4%) in the *H. pylori* treatment cohort received a PPI-clarithromycin-containing triple therapy.

Recent retrospective cohort studies reported inconsistent results for the association between clarithromycin-containing *H. pylori* treatment and overall mortality.[25-27] Mosholder et al.[25] showed that overall mortality was increased during a median follow-up of 3.1 years after clarithromycin-containing *H. pylori* treatment when compared with the metronidazole regimen (aHR, 1.09; 95% CI, 1.00 to 1.18). In contrast, Root et al.[26] reported that overall mortality (adjusted incidence risk rate [aIRR], 0.97; p=0.66) and cardiovascular mortality (aIRR, 0.93; p=0.69) were not increased in the 3 years after *H. pylori* treatments. Interestingly, Andersen et al.[27] reported that patients with ischemic heart disease who received *H. pylori* treatment had an increased risk of overall mortality for 1 year (HR, 1.50; p< 0.0001), but no increase in the overall mortality risk (HR, 1.02; p=0.87) during 5-year periods. These studies included patients who had cardiovascular diseases (coronary heart disease/ischemic heart disease, heart failure/cardiomyopathy, or arrhythmia) at baseline, which

Table 3. Risk of Incidence for Cardiovascular Diseases, Cerebrovascular Diseases, and Cancer Stratified by *H. pylori* Treatment

	Incidence, no. (%)		Risk of incidence for *H. pylori* treatment cohort*			
	H. pylori treatment group (n=5,541)	Control group (n=11,082)	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Cardiovascular disease	714 (12.9)	1,232 (11.1)	1.18 (1.07–1.29)	<0.001	1.13 (1.03–1.24)	0.01
Cerebrovascular disease	408 (7.4)	814 (7.3)	1.00 (0.89–1.13)	0.962	0.98 (0.87–1.11)	0.657
Overall cancers	429 (7.7)	737 (6.7)	1.18 (1.04–1.32)	0.008	1.14 (1.01–1.28)	0.035
Stomach cancer	54 (1.0)	87 (0.8)	1.24 (0.89–1.75)	0.209	1.26 (0.90–1.78)	0.182
Non-stomach cancer	381 (6.9)	659 (6.0)	1.17 (1.03–1.32)	0.017	1.12 (0.99–1.27)	0.078
Oral cancer	15 (0.3)	19 (0.2)	1.58 (0.80–3.11)	0.185	1.60 (0.81–3.18)	0.175
Esophageal cancer	3 (0.1)	7 (0.1)	0.86 (0.22–3.31)	0.823	0.82 (0.21–3.20)	0.771
Colorectal cancer	67 (1.2)	95 (0.9)	1.42 (1.04–1.93)	0.03	1.39 (1.01–1.90)	0.043
Liver cancer	48 (0.9)	101 (0.9)	0.95 (0.67–1.34)	0.774	0.83 (0.59–1.18)	0.295
Biliary tract cancer	5 (0.1)	17 (0.2)	0.59 (0.22–1.59)	0.297	0.59 (0.22–1.61)	0.302
Pancreatic cancer	21 (0.4)	31 (0.3)	1.36 (0.78–2.36)	0.282	1.25 (0.71–2.19)	0.435
Lung cancer	34 (0.6)	67 (0.6)	1.02 (0.67–1.53)	0.942	0.99 (0.65–1.49)	0.942
Breast cancer	12 (0.2)	24 (0.2)	1.00 (0.50–2.00)	1.000	0.98 (0.49–1.97)	0.956
Prostate cancer	58 (1.0)	101 (0.9)	1.15 (0.83–1.59)	0.397	1.13 (0.81–1.56)	0.472
Bladder cancer	6 (0.1)	17 (0.2)	0.71 (0.28–1.79)	0.462	0.70 (0.27–1.79)	0.456
Thyroid cancer	42 (0.7)	53 (0.5)	1.59 (1.06–2.38)	0.025	1.54 (1.03–2.32)	0.037
Brain, CNS cancer	3 (0.1)	6 (0.1)	1.00 (0.25–4.00)	1.000	0.87 (0.22–3.50)	0.841
Non-Hodgkin lymphoma	3 (0.1)	4 (0.04)	1.50 (0.34–6.70)	0.595	1.39 (0.31–6.30)	0.667
Leukemia	5 (0.1)	3 (0.03)	3.34 (0.80–13.97)	0.099	3.51 (0.83–14.89)	0.089

H. pylori, *Helicobacter pylori*; HR, hazard ratio; CI, confidence interval; CNS, cerebral nervous system.
*HR obtained using the Cox proportional hazard model. In the multivariate analyses, the covariates included were age, sex, economic status, residential area, Charlson comorbidity index score, and aspirin and statin use.

might have affected cardiovascular mortality risk.[25-27] Gastroenterologists may be reluctant to prescribe a clarithromycin-containing *H. pylori* treatment for patients with cardiovascular diseases. To avoid selection bias and short-term cardiovascular effects of clarithromycin, we excluded patients with cardiovascular diseases other than hypertension before baseline and up to 6 months after *H. pylori* treatment.

Antibiotic treatment can cause dysbiosis and may alter the beneficial roles of gut microbiota in the modulation of carcinogenesis, response to cancer treatment including chemotherapy, immunotherapy and radiotherapy, and treatment-related toxicities.[10,11] Repeated macrolide antibiotic exposure was significantly associated with increased risks of lung, gastric, biliary, and kidney cancer.[12] Our recent randomized trial also showed that the *H. pylori* treatment group had a nonsignificantly higher risk of non-gastric cancer death compared with the placebo group (3.1% vs 0.5%, respectively; p=0.06).[20] In the current study, *H. pylori* treatment was significantly associated with overall cancer incidence risk (aHR, 1.14; p=0.035), especially colorectal cancer and thyroid cancer incidences. However, mortality risk due to overall cancer and non-gastric cancer did not increase after *H. pylori* treatment. We speculated the finding that increased overall cancer incidence was not accompanied by a corresponding

mortality increase after *H. pylori* treatment might be explained by the bias associated with health behavior difference between cohorts. Patients in the treatment cohort had higher proportions of metropolitan residency, better economic status levels, and tended to use statin. In addition, some portions of patients (~5%) received *H. pylori* treatment without peptic ulcer disease and these patients might be treated for prophylactic eradication. Thus, the *H. pylori* treatment cohort might be more likely to attend a health examination or cancer screening program. This is supported by the finding that the incidences of colorectal cancer and thyroid cancer were both significantly increased, and both are well-known for screening-related incidence increase.[28,29] However, we could not evaluate whether the stages of diagnosed colon cancer or thyroid cancer were affected according to the health behavior differences because the database did not provide cancer stage information.

Two recent meta-analyses reported inconsistent results regarding the association between *H. pylori* infection status and cerebrovascular disease risks.[30,31] A meta-analysis of case-control studies showed a significant association between *H. pylori* infection status and increased risk of ischemic stroke,[30] but the meta-analysis of prospective cohort studies reported that *H. pylori* infection status did not increase stroke risk.[31] Meanwhile,

Table 4. Risk of Cause-Specific Mortality Stratified by *H. pylori* Treatment

	Death, No. (%)		Risk of mortality for *H. pylori* treatment cohort*			
	H. pylori treatment group (n=5,541)	Control group (n=11,082)	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Overall	229 (4.13)	608 (5.49)				
Cardiovascular disease	18 (0.32)	34 (0.31)	1.06 (0.60-1.88)	0.842	0.96 (0.54-1.71)	0.896
Cerebrovascular disease	15 (0.27)	66 (0.60)	0.45 (0.26-0.79)	0.006	0.46 (0.26-0.81)	0.007
Overall cancers	68 (1.23)	170 (1.53)	0.80 (0.60-1.06)	0.112	0.76 (0.57-1.01)	0.058
Stomach cancer	6 (0.11)	10 (0.09)	1.20 (0.44-3.30)	0.724	1.21 (0.44-3.38)	0.71
Non-stomach cancer	62 (1.12)	160 (1.44)	0.77 (0.58-1.03)	0.083	0.73 (0.55-0.99)	0.04
Oral cancer	0	2 (0.02)	NA		NA	
Esophageal cancer	2 (0.04)	3 (0.03)	NA		NA	
Colorectal cancer	5 (0.09)	17 (0.15)	0.59 (0.22-1.59)	0.297	0.60 (0.22-1.64)	0.319
Liver cancer	12 (0.22)	45 (0.41)	0.53 (0.28-1.01)	0.052	0.48 (0.25-0.91)	0.024
Biliary tract cancer	5 (0.09)	13 (0.12)	0.77 (0.27-2.16)	0.618	0.79 (0.28-2.22)	0.65
Pancreatic cancer	5 (0.09)	13 (0.12)	0.77 (0.27-2.16)	0.618	0.67 (0.24-1.91)	0.456
Lung cancer	15 (0.27)	32 (0.29)	0.94 (0.51-1.73)	0.836	0.95 (0.51-1.75)	0.857
Breast cancer	0	1 (0.01)	NA		NA	
Prostate cancer	0	4 (0.04)	NA		NA	
Bladder cancer	0	7 (0.06)	NA		NA	
Thyroid cancer	1 (0.02)	0	NA		NA	
Brain, CNS cancer	0	1 (0.01)	NA		NA	
Non-Hodgkin lymphoma	1 (0.02)	3 (0.03)	NA		NA	
Leukemia	3 (0.05)	1 (0.01)	NA		NA	

H. pylori, *Helicobacter pylori*; HR, hazard ratio; CI, confidence interval; CNS, cerebral nervous system; NA, not available.
*HR obtained using the Cox proportional hazard model. In the multivariate analyses, the covariates included were age, sex, economic status, residential area, Charlson comorbidity index score, and aspirin and statin use.

in a recent population-based study, subgroup analysis including patients who received *H. pylori* eradication showed that stroke risk was not increased after the clarithromycin-containing *H. pylori* treatment.[23] Similarly, we found that cerebrovascular disease risk was not increased after *H. pylori* treatment (aHR, 0.98; p=0.657). However, mortality risk due to cerebrovascular disease was significantly decreased by 54% after *H. pylori* treatment. The reason for the lower cerebrovascular mortality risk in the *H. pylori* treatment group remains unclear.

Our study has several limitations associated with an observational study of a retrospective cohort study design. First, our study population was hypertension patients and our results might not be applicable to the general population with no cardiovascular risk. Second, the ICD-10 disease codes for hypertension were used for selection of the study population from the database, and possible upcoding for hypertension diagnosis could not be completely excluded. However, to reduce the possibility, we only selected patients who had a prescription for an anti-hypertensive drug. Third, our analysis was based on the prescription of *H. pylori* treatment regimen. Neither actual compliance with the prescribed drugs nor *H. pylori* status after treatment was available from the database. Also, the nontreatment

cohort included patients who might be infected but not treated and those who were not infected. Fourth, the use of antithrombotic agents or antiplatelet agents other than aspirin which might affect the study outcomes was not included, because proportions of preventive use of such agents other than aspirin or statin might be low in our study patients who had not been previously diagnosed with cardiovascular diseases or cerebrovascular diseases before *H. pylori* treatment. Fifth, the proportion of patients who received only bismuth-containing quadruple therapy was 1.3%, and majority of the study outcomes might derive from the effects of PPI-clarithromycin containing triple therapy. Finally, lifestyle factor variables present at baseline such as smoking, alcohol, or body mass index that might affect incidence and mortality of our study outcome diseases were frequently missing from the available dataset.

In conclusion, *H. pylori* treatment in patients with hypertension was not significantly associated with increased overall mortality. When analyzed by the major causes of death, *H. pylori* treatment did not increase mortalities due to cardiovascular diseases, cerebrovascular diseases, or overall cancers. Further prospective studies are needed to confirm these findings before implementing a policy of *H. pylori* eradication for the purpose

of gastric cancer prevention in general populations.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Interpretation of the data: Y.I.K., Y.A.K., I.J.C. Drafting of the article: Y.I.K., I.J.C. Statistical analysis: Y.A.K., J.W.L. Conception and design of study: I.J.C. Critical revision for important intellectual content and final approval of the manuscript: Y.I.K., Y.A.K., J.W.L., H.J.K., S.H.K., S.G.K., J.I.K., J.J.K., I.J.C.

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